

REMARKS

Claims 1-4, 6, 8-14, 17-18, and 26-27 are pending in the application. Claims 12-14 were previously withdrawn without prejudice. Claims 5 and 19-25 were previously cancelled. Claims 8-11 are cancelled within without prejudice. In the instant response, claim 1 has been amended. Applicant reserves the right to pursue the cancelled claims in a continuing application. Support for the amendment to claim 1 can be found throughout the specification, for example in Examples 1 and 2 and in claims 8-11. Upon entry of the instant amendment, claims 1-4, 6, 17-18, and 26-27 will be before the Examiner for consideration.

Withdrawal of objections and/or rejections

Applicant thanks the Examiner for withdrawal of all of the previous rejections for obviousness in the instant case.

Rejections Under 35 U.S.C. §112, second paragraph

The Office Action has rejected claims 1-4 and 17-18 under 35 U.S.C. §112, ¶2 for allegedly failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention. The Office Action asserts that the phrase “differentiating inducing conditions” is vague and unclear.

Applicant respectfully disagrees, however, purely to progress the prosecution of the application, Applicant has amended claim 1 as set forth above to incorporate the limitations of claims 8-11, not included in the instant rejection, and to recite that differentiation inducing conditions comprise “culturing the pluripotent stem cells for one to two months in a culture medium comprising fetal calf serum, avian serum, epidermal growth factor (EGF), and fibroblast growth factor 2 (FGF2).” This amendment complies with the suggestion of the Examiner to amend the claim to recite specific growth conditions. Withdrawal of the rejection is respectfully requested.

*Rejections Under 35 U.S.C. §112, first paragraph*Enablement

The Office Action has rejected claims 1-4, 6, 17-18, and 26-27 under 35 U.S.C. §112, first paragraph for allegedly not being enabled for being overly broad. However, the Office Action states that “the specification... [is] enabling for a method for producing myocardial cells comprising isolation of ... IPE... and performing adherent culturing... with DMEM/F12, DMEM or EMEM, comprising FGF, EGF or CNTF and serum.” Without agreeing with the rejection, Applicant has amended claim 1 as set forth above to include all of the limitations of claims 8-11, not included in the instant rejection. This amendment was suggested by the Examiner and to conforms to the scope of the invention stated to be enabled by the Examiner. Withdrawal of the rejection is respectfully requested.

Written Description

The Office Action has rejected claims 1-4, 6, 8-11, 17-18, and 26-27 under 35 U.S.C. §112, first paragraph for allegedly not meeting the requirement for written description. The Office Action asserts that the only methods comprising differentiation conditions provided in the instant application include culturing of cells in “DMEM, EMEM, growth factors like EGF, FGF2, serum like fetal calf serum and avian serum, and serum free culture media of DMEM/F12 with N2 supplement.” Without agreeing with the Examiner, Applicant has amended the claim to recite the embodiment of the invention stated to be supported in the specification. Withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

The Office Action has rejected claims 1-4, 6, 8-11, 17-18, and 26-27, all of the claims under examination in the instant application, as allegedly being unpatentable over Kosaka et al. (hereinafter Kosaka) in view of Tropepe et al. (hereinafter Tropepe) and further in view of Pardo et al. (hereinafter Pardo) as evidenced by Reynolds et al. (hereinafter Reynolds).

Applicant respectfully disagrees and traverses the rejection.

The claims have been amended as set forth above to recite that "the pluripotent stem cells one to two months in a culture medium comprising fetal calf serum, avian serum, EGF, and FGF2". These differentiation conditions for obtaining the myocardial cells from the pluripotent stem cells cultured by the floated coagulated mass culturing technique cannot be obvious in view of the cited references.

These specific differentiation inducing conditions are neither disclosed nor suggested in Kosaka, Tropepe, Pardo, or Reynolds and Weiss which form the basis of the rejection. Since none of the cited documents discloses or suggests the specific differentiation inducing conditions now claimed, the presently claimed invention cannot be obvious in view of a combination of the cited documents.

Moreover, the invention of the amended claim provides an unique effect that the myocardial cells can be obtained from the pluripotent stem cells derived from the iris pigmented epithelial cells cultured by the floated coagulated mass culturing technique.

The Court has considered obviousness in chemical cases post-*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

While the *KSR* Court rejected a rigid application of the... TSM test in an obviousness inquiry, the Court acknowledged the importance of identifying '**a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does**' in an obviousness determination.

When there is a design need or market pressure to solve a problem and there is **a finite number of identified, predictable solutions**, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. * * * That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. *Takeda Chemical Industries Ltd. v. Alphapharm Pty.* 492 F.3d 1350 (Fed. Cir. 2007) [emphasis added]

Applicant submits that the combination of references could only have been made in hindsight. The number of references teaching cell culture methods for any of a number of purposes cannot be considered to provide "a finite number of predictable

solutions." Moreover, no specific design need or market pressure can be identified to establish the instantly claimed method to generate myocardial cells from IPE cells.

The MPEP section 2143.01 provides guidance regarding the combination of references to provide a proper obviousness rejection.

[III.] The mere fact that references can be combined or modified does not render the resultant combination obvious ***unless >the results would have been predictable to one of ordinary skill in the art.*** *KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007)("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.").<

[IV.] A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" ***because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references.*** *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). >[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).<

Contrary to the assertion in the Office Action that the combination of methods and reagents simply provide the expected effect, the cited references provide different teachings. Further, the teachings of the references as a whole would teach one that culture conditions useful for the culturing of one cell type would not necessarily be useful for the culturing of another cell type.

The second column on page 245 of Kosaka states:

The efficiency of transdifferentiation of PE cells and the periods of cultivation required for transdifferentiation to occur have not always been constant even in the same medium. These unexpected facts have made it difficult to systematically analyze transdifferentiation at a molecular level. In addition to attempts to modify culture conditions to enable more

effective culture of the RPE cells, we also sought other sources of PE cells.

Therefore, Kosaka teaches that:

1. Culturing primary cells is difficult;
2. Selection of growth conditions and growth media cannot be predicted; and
3. Growth and maintenance of two highly related primary cell cultures, RPE cells and IPE cells, are drastically different, one being highly unpredictable, and one being predictable under at least one set of growth conditions.

Kosaka teaches growth and maintenance of IPE cells in EMEM supplemented with dialyzed FBS, to remove small proteins such as growth factors and glutamine. Kosaka teaches the use of phenylthiourea to decrease melanin production and promote de-differentiation of cells and formation of a confluent monolayer of flattened cells (page 246, col 2) for differentiation into lens by adding ascorbic acid. This specific method of promoting de-differentiation would not be expected to be useful except in cells producing high levels of melanin, such as PE cells. As Kosaka teaches that selection of cell type and selection of cell growth conditions must be carefully done, it would not be obvious how one could modify Kosaka to provide the instantly claimed invention.

Based on the teachings of Kosaka regarding the substantial differences in culturing IPE cells and RPE cells, one would not look to a reference such as Tropepe teaching the culturing of PCM for modifications of methods and reagents for culturing IPE cells as claimed. Tropepe does not teach de-differentiation or differentiation of cells, but instead simply teaches culturing cells. Such a reference can provide no teachings or suggestions in relation to the instantly claimed methods that provide for the transdifferentiation of IPE cells to myocardial cells. Further, Tropepe teaches the use of defined media containing progesterone, putrescine, and selenium salt which would not likely have been present in the culture media as they are small molecules and would have been dialyzed out of the bovine serum if they had even been present in the first place. After careful selection of growth conditions relying on serum containing media, one would not look to a reference teaching serum free media.

Pardo teaches the aggregation of primary neuronal cultures in brain. Again, Pardo provides no teachings regarding transdifferentiation which is an essential element of the claimed invention. The simple existence of a method to form cell aggregates by rotation does not provide a motivation to modify either Kosaka or Tropepe to provide the instantly claimed invention. Further, the fact that some of the media supplements taught by Pardo are present in N2 supplement, does not provide a motivation to culture cells without all of the components taught by Pardo (page 85, Materials and Methods section).

It is further noted that the instantly claimed method requires growth first in serum free media followed by growth in serum containing media. This method cannot be obvious in view of the cited art.

Therefore, the invention described in the amended claim 1 and the dependent claims thereof are not attainable even by combining the cited references, and thereby being non-obvious over the cited references.

Therefore, the invention as claimed cannot be considered obvious in view of any of the cited references. Withdrawal of the rejection is respectfully requested.

Conclusion:

In view of the amendments and arguments presented herein, Applicants submit that the claims are in condition for allowance.

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Respectfully submitted,

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